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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,543	05/26/2000	Beatrice Gaugler	LUD 5353.5 (10016355)	7364

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,543	GAUGLER ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-58,60,61 and 63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-58, 60, 61 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the action mailed June 27, 2003 has been withdrawn and PROSECUTION IS HEREBY REOPENED. A new action is set forth below.

2. Claims 38-58, 60, 61 and 63-66 are pending.

Claims 38-58, 60, 61 and 63-66 are examined on the merits.

3. The supplemental declaration, which lists three inventors instead of four inventors, as listed in the originally filed declaration is acceptable as supported by MPEP § 201.03.

Claim Objections

4. Claim 58, line 2 is objected to because of the following informality: the claim recites "a tumor rejection antigen precursor encoded by *nucleotides* 13". Correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 38-58, 60, 61 and 63-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth SEQ ID NO: 13 (gene for MAGE-4), 14 (gene for MAGE-41) and SEQ ID NO: 15 (cDNA for MAGE-4). The written description is not commensurate with the broad scope of the claims drawn to

(a) polynucleotides which encode a tumor rejection antigen precursor and a part of a tumor rejection antigen precursor, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleic sequence set forth in SEQ ID NO: 13, 14 or 15 and fragments of the said sequences;

(b) polynucleotides, as well as cDNA molecules which encode a fragment (including those processed by a cell) of tumor rejection antigen precursor, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleotide sequence set forth in SEQ ID NO: 13, 14 or 15 and fragments of the said sequences;

(c) polynucleotides which encode a tumor rejection antigen, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleic sequence set forth in SEQ ID NO: 13, 14 or 15; and

(d) isolated DNA molecules which encode a MAGE-4 or MAGE-41 tumor rejection antigen precursor comprising fragments of SEQ ID NO: 13, 14 or 15, as well as the vectors and host cells that contain all of the said polynucleotides of (a)-(b). The specification does not provide sufficient written description of MAGE tumor antigen precursors as broadly claimed. The broad claims are based upon the limited

disclosure/recitation of a limited number of nucleic acids encoding a specific MAGE-4 or MAGE-41. There is insufficient written description of the structural attributes that define or distinguish a MAGE tumor rejection antigen precursor, including MAGE-4 and MAGE-41 tumor rejection antigen precursors from one another or other molecules. However, it is noted that the structure (e.g. sequences) of MAGE molecules differ from one another and that such MAGE molecules are classified as separate molecules (e.g. MAGE-4 and MAGE-41).

It is established in the art that "MAGE-1 belongs to a family of closely related genes. This makes it impossible to evaluate its expression by hybridization of Northern blots with large probes, because these probes cross-hybridize with other genes of the MAGE family. However, expression of MAGE-1 can be measured specifically by reverse transcription and polymerase chain reaction (PCR) using oligonucleotide primers corresponding to MAGE-1 sequences that display several differences with the corresponding sequences of the other MAGE genes.",. see Brasseur et al. (Int. J. Cancer 52: 839-841, 1992).

Furthermore, the high degree of homology shared among members of the MAGE gene family makes it difficult to distinguish one MAGE tumor rejection antigen precursor (e.g. MAGE-1) from the other MAGE gene family members. For example, nucleic acid molecules, which hybridize to SEQ ID NO: 13, 14 or 15 will not necessarily define any particular tumor antigen precursor.

Given the polymorphism and homology of MAGE tumor rejection antigen precursors there is insufficient written description of the alternative or allelic forms of

MAGE tumor rejection antigen precursors encoded by nucleic acids which hybridize to SEQ ID NO: 13, 14 or 15 under the written description provision of 35 USC 112, first paragraph.

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function.", see page 367, column 2, paragraph 2.

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB Journal 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells (see page 2251, column 1, paragraph 1 of Tumor Antigens). Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty.", see page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They

are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the recognition of a very low density of antigenic peptides bound to class I molecules" (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence", see page 28, column 1.

Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence.

In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursor, given the homology and diversity of MAGE molecules and given the lack of correlation with between a particular structure(s) of a MAGE tumor rejection antigen precursor and its ability to increase an anti-tumor cytotoxic T lymphocyte response, particularly in vivo.

The instant application does not provide sufficient guidance as to the nexus or correlation between the structure and function of a MAGE tumor rejection antigen encoded by the claimed nucleic acid molecules that places the skilled artisan in possession of the relevant identifying characteristics of a genus of MAGE tumor rejection antigen precursors encoded by the myriad of nucleic acid molecules, commensurate in scope with the claimed invention.

Therefore, only the SEQ ID NOS: 13, 14 and 15 provide for the nucleic acid sequences of MAGE-4 and MAGE-41 tumor rejection antigen precursor meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The specification does not provide sufficient written description of a tumor antigen precursor based upon the limited disclosure/recitation of a one nucleic acid encoding each different MAGE tumor antigen precursor. There is insufficient written description of the structure / sequences of nucleic acids or complementary sequences of which hybridize to SEQ ID NO: 13, 14 or 15 and encode a MAGE tumor antigen precursor and, in turn, provide the appropriate structural and functional attributes of a MAGE tumor antigen precursor. Therefore conception is not achieved until reduction to

practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

In the absence of structural characteristics that are shared by members of the genus of MAGE tumor rejection antigen precursors encoded by the myriad of claimed nucleic acid molecules commensurate in scope with the claimed invention; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Only nucleic acids defined as SEQ. ID. NO: 13, 14 and 15 consisting of specific nucleic acid residues, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph.

7. Claims 38-58, 60, 61 and 63-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid sequences identified as MAGE-4 (SEQ ID NO: 13 and 15) and MAGE-41 (SEQ ID NO: 14), does not reasonably provide enablement for any isolated nucleic acid molecule which encodes a tumor rejection antigen, precursor or a fragment thereof, wherein the complementary sequence of said isolated nucleic acid hybridizes to a nucleotide sequence set forth as SEQ ID NO: 13, 14 or 15 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. nucleic acid or amino acid sequences) that distinctly identifies the breadth of MAGE tumor rejection antigens encoded by nucleic acids encoding tumor rejection antigen precursors which hybridize to SEQ ID NO: 13, 14 or 15, encompassed by the claimed invention.

Applicant should limit the claims either to SEQ ID NO: 13, 14 or 15 which read on MAGE-4 and MAGE-41.

While the recitation of "tumor antigen precursor" may have some notion of the properties of the claimed molecule(s), claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use the "tumor antigen precursors", commensurate in scope with the claimed invention.

There is insufficient guidance and direction as to how to make and use the breadth of MAGE tumor rejection antigen precursors encoded by nucleic acids that hybridize to SEQ ID NO: 13, 14 or 15; other than MAGE-4 and MAGE-41 encoded by SEQ D NO: 13, 14 and 15 in the absence of structural or functional attributes that define a MAGE tumor rejection antigen precursor.

A person of skill in the art is not enabled to make and use the breadth of MAGE tumor rejection antigen precursors, which can be processed to form the presentation of tumor rejection antigens and be characteristic of a particular tumor, commensurate in scope with the claimed invention. The skilled artisan would not have predicted that all that is required for a tumor antigen precursor is that it can be encoded by a nucleic acid of which hybridizes to SEQ ID NO: 13, 14 or 15. A skilled artisan would have expected that other structural and functional attributes would be required to provide for a nucleic acid to encode a MAGE tumor rejection antigen precursor and its ability to be processed to form a tumor rejection antigen characteristic of a particular tumor.

The instant specification discloses in Example 30 that the cDNA sequence for MAGE-4 was identified by a 2.4kb fragment, see page 34, lines 33-37. The specification seems to be silent on the full description of MAGE-41. Here, the specification does not enable the breadth of MAGE tumor rejection antigen precursors encoded by the myriad of nucleic acid molecules that hybridize to SEQ ID NO: 13, 14 or 15 as broadly claimed based upon the limited disclosure/recitation that the said SEQ ID numbers encodes MAGE-4 and MAGE-41. There is insufficient guidance and direction as to the structural attributes that define or distinguish MAGE tumor rejection antigen precursors.

As noted by Brasseur "MAGE-1 belongs to a family of closely related genes. This makes it impossible to evaluate its expression by hybridization of Northern blots with large probes, because these probes cross-hybridize with other genes of the MAGE family. However, expression of MAGE-1 can be measured specifically by reverse transcription and polymerase chain reaction (PCR) using oligonucleotide primers corresponding to MAGE-1 sequences that display several differences with the corresponding sequences of the other MAGE genes.",. see Brasseur et al. (Int. J. Cancer 52: 839-841, 1992). This is consistent with the instant application as filed wherein the specification discloses, "... that the expression of particular MAGE genes is not always linked to particular disorders, or individuals of particular HLA types.", see page 7, lines 15-20.

Given the polymorphism and homology of MAGE tumor rejection antigen precursors, there is insufficient enablement of implementation in cancer vaccines and

therapeutic treatments encompassing the claimed alternative and allelic forms of MAGE tumor rejection antigen precursors, including MAGE-4 and 41 tumor rejection antigen precursors encoded by nucleic acids which hybridize to SEQ ID NO: 13, 14 or 15 commensurate in scope with the claimed invention.

In discussing the perspectives of specific immunotherapy with tumor antigens, including MAGE-1, co-inventor Boon acknowledges that: "While these are exciting prospects, it is difficult to predict whether therapeutic success will be achieved, even if a significant increase in anti-tumor CTL is obtained by immunization" (Int. J. Cancer 54: 177-180, 1993; see entire document, particularly, page 178, column 2, paragraph 2).

Applicant appears to rely upon that these tumor rejection antigens and precursors that encode the MAGE proteins of the claimed invention. However, even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al. (APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

And the high degree of homology shared among members of the MAGE gene family makes it difficult to distinguish one MAGE molecule (e.g. MAGE-1) from the other

MAGE gene family members, see page 5, column 1, second paragraph of Zakut et al. (Cancer Research 53: 5-8, January 1, 1993).

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see De Plaen et al., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column1, paragraph 2).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the processing and presentation of MAGE-derived peptides in an attempt to obtain cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this

group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB Journal 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty□ (page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the

recognition of a very low density of antigenic peptides bound to class I molecules□ (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence" (page 28, column 1).

Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence.

In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursors (e.g. MAGE-1), given the homology and diversity among MAGE molecules and given the lack of correlation with between a particular structure(s) between a MAGE tumor rejection antigen precursor and its ability to increase an anti-tumor cytotoxic T lymphocyte response, particularly in vivo.

The instant application does not provide sufficient guidance as to the nexus or correlation between the structure and function of MAGE tumor rejection antigen precursors that enables the skilled artisan to predict the relevant identifying

characteristics of a genus of MAGE tumor rejection antigen precursors which hybridize to SEQ ID NO: 13, 14 or 15.

A person of skill in the art could not predict which particular nucleic acids other than that was set forth in SEQ ID NO: 13, 14 or 15 would be sufficient to confer the ability to encode a MAGE tumor antigen precursor and, in turn, wherein the MAGE tumor antigen precursor can be processed to form a tumor rejection antigen characteristic of a particular tumor

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using tumor antigen precursors encoded by nucleic acids of which the complementary sequence hybridizes to SEQ ID NO: 13, 14 or 15, wherein the appropriate structural and functional features of a MAGE tumor antigen precursor (e.g. MAGE) would be maintained would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The examiner works a flexible schedule, however can normally be reached between the hours of 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne "Bonnie" Eyler, Ph.D. can be reached on (571) 272-0871. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.

20 April 2004

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